REMARKS

Claims 1, 2, 10-14 and 28-82 are all the claims pending in the application; each of the claims has been rejected.

No new matter has been added. Entry of this Response is respectfully requested.

I. Formal Matters

A. As noted in the Amendment filed September 26, 2003 in this application, the Examiner has not provided Applicants with a complete copy of the initialed and signed reference list submitted with the IDS filed in this application on February 11, 2002. Therefore, Applicants again renew their request for an appropriately acknowledged copy of the missing page, and include a copy of the missing page herewith for the Examiner's convenience.

B. Similarly, while Applicants requested the Examiner to acknowledge Applicant's claim for domestic priority to U.S. provisional application number 60/268,326, filed February 14, 2001, the Examiner neglected to do so. Therefore, Applicants again renew their request for such acknowledgement to be made in the next paper issued by the U.S. PTO.

II. Rejection of Claims Under 35 U.S.C. §112

A. At paragraph 4 of the Office Action, claims 28-45 and 67-82 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description support.

The Examiner states that the claims are rejected over the recitation of the negative limitations "an extrinsic fluorescent marker is not part of the system." The Examiner explains that negative limitations must have support in the original disclosure and that the mere absence of a positive recitation is not a basis for exclusion.

In response, Applicants respectfully refer the Examiner to MPEP §2173.05(i) wherein it is stated that "if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims."

There is clear support in the specification for use of alternative elements, i.e., an unlabeled biomolecule (i.e., measurement of intrinsic emission) as well as a fluorophore-labeled biomolecule (i.e., measurement of extrinsic emission).

For example, it is stated at page 3, line 27, through page 4, line 4, of the specification that:

> 1. It will be appreciated by one of ordinary skill in the art that the scope of the present invention includes increasing the intrinsic fluorescence as well as the fluorescence of a biomolecule labeled with extrinsic probes. The extrinsic fluorescence of a biomolecule includes but is not limited to the fluorescence of a fluorophore conjugated to the biomolecule. Such extrinsic fluorophores can be covalently or non-covalently attached to the biomolecule.

Moreover, examples of extrinsic fluorophores are given at page 11, lines 7-23 (e.g., FITC ethidium bromide). Examples of intrinsic fluorophores are provided at page 11, lines 24-29 (e.g., DNA, RNA, proteins, peptides). Examples of biomolecules are provided at page 12, lines 1-9 and include DNA, RNA, proteins, peptides. Thus, biomolecules are themselves also intrinsic fluorophores.

Furthermore, page 14 (paragraphs 68 and 69) there is a discussion of the differences between measurement of intrinsic and extrinsic fluorescence. Similarly, it is stated at page 16, paragraph 76, that "the present invention discloses a novel method for the detection of nucleic acid sequences by increasing the intrinsic fluorescence of the nucleic acids." As further stated in the same paragraph, "the present invention does not require the use of an extrinsic probe."

Additionally, it is stated that "it will be appreciated that the detection of the nucleic acid can be based on increasing the fluorescence intensity of an extrinsic fluorophore attached to a nucleic acid by positioning the fluorophore adjacent to a metal particle."

In paragraph 77, lines 19-21, it is stated that "the identification of nucleic acids using the intrinsic fluorescence of the nucleic acid eliminates the requirement for extrinsic probes." In paragraph 79 is a discussion of another embodiment of the invention where an extrinsic fluorophore is used.

Thus, it is clear that "alternative elements are positively recited" in the specification, as contemplated by MPEP §2173.05(i), where, as indicated above, it is stated that "if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims."

Therefore, Applicants respectfully traverse the Examiner's position that the claims reciting negative limitations do not have support in the original disclosure, and request reconsideration and withdrawal of this rejection.

B. At paragraph 5 of the Office Action, claims 1, 2 and 10-14 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description support.

The Examiner states that the recitation of "single metal particle" in claims 1, 2, 10, 11, 13 and 14 is a limitation that is not supported in the specification.

In response, Applicants respectfully traverse the Examiner's position and note that the specification supports use of a "single metal particle." For example, at page 3, lines 17-20, it is stated that "one aspect of the present invention is directed to a biomolecule in combination with a metal particle, where the metal particle and the biomolecule are positioned..." It is clear that "a

metal particle" is singular, and thus is equivalent to a "single metal particle." Indeed, there are a large number of descriptions in the specification where "a metal particle" is disclosed (see, e.g., paragraphs 98-100). The fact that there are also a large number of descriptions where the plural form of the word (i.e., metal particles) is used (see, e.g., page 13, lines 9-11), makes it clear that both single metal particles, and multiple metal particles are taught in the instant specification.

Furthermore, the skilled artisan can easily conceive of a number of instances where a single metal particle would be desirable. For example, in a probe of a library, a single probe (joined to a metal particle) could be used to identify a single locus within the library.

For these reasons, it is clear that the recitation of a "single metal particle" in claims 1, 2, 10, 11, 13 and 14 is a limitation that is fully supported in the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Rejection of Claims Under 35 U.S.C. §102

At paragraph 7 of the Office Action, claims 1-2 and 10-14 are rejected under 35 U.S.C. §102(b) as being anticipated by Schalkhammer et al. (USSN 5,866,433).

The Examiner repeats the analysis of Schalkhammer et al. set forth in the previous Office Action, dated March 27, 2003, as his basis for rejecting these claims.

In response, Applicants first note that the rejected claims recite a system comprising one or more biomolecules and a single metal particle. Furthermore, in the amendment filed September 26, 2003, Applicants noted the following at pages 12-13:

> With regard to pending claims 1-2 and 10-14, these claims are directed to a system comprising one or more biomolecules in combination with a "single" metal particle. In contrast, a close reading of Schalkhammer et al. reveals that the sensor taught

> therein makes use of multiple metal particles in every embodiment of the sensor.
>
> As Schalkhammer et al. does not teach or suggest a sensor using only one metal particle, as recited in claims 1-2 and 10-14 of the present application, Schalkhammer et al. does not anticipate the cited claims and Applicants respectfully request reconsideration and withdrawal of this rejection.

In the instant Office Action, the Examiner states that the arguments are not persuasive. In particular, the Examiner states that "Applicant argues that because Schalkhammer et al. has a preferred embodiment of multiple metal particles, Schalkhammer et al. is limited to the preferred embodiment."

Applicants respectfully assert that they did not state that "Schalkhammer et al. has a preferred embodiment of multiple metal particles" but instead stated that Schalkhammer et al. "makes uses of multiple metal particles in every embodiment of the sensor." Thus, Schalkhammer et al. only provides embodiments where multiple metal particles are used. There is no teaching or suggestion of the use of a single metal particle, in any embodiment, much less a non-preferred embodiment of Schalkhammer et al..

The Examiner goes on to cite to *In re Susi* and the discussion thereof in MPEP §2123 for the idea that "disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments." The Examiner further states that "it is clear that simply because Schalkhammer et al. has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and this does not constitute teaching away."

Applicants note that MPEP §2123 merely supports the idea that non-preferred embodiments still constitute prior art. Respectfully, however, this rule is not relevant here.

While any non-preferred embodiments of Schalkhammer et al. could potentially be prior art against the rejected claims, it is important to note that none of the embodiments of Schalkhammer et al. teach or suggest the use of a single metal particle, preferred or non-preferred. All embodiments of Schalkhammer et al. make use of multiple metal particles.

The Examiner goes on to state that "in this case, any single particle (as suggested by Schalkhammer that changing the number or size of the metal particles are nothing but routine optimization) under any suitable condition can be used to detect a biomolecule" (sentence bridging pages 8-9). The Examiner appears to be arguing that it would have been obvious to use a single metal particle in the invention of Schalkhammer et al.

Applicants respectfully remind the Examiner that in order for a reference to serve as prior art under 35 U.S.C. §102(b), it must teach each element of the claimed invention. Schalkhammer et al. clearly does not teach the use of a single metal particle. Whether the individual metal particles of Schalkhammer et al. each individually have the properties inherent in the other metal particles has no bearing on the analysis. Because Schalkhammer et al. does not teach the use of a single metal particle, it does not anticipate Applicant's invention.

Whether Schalkhammer et al. *suggests* the invention recited in the rejected claims is not a question to be considered under 35 U.S.C. §102(b). However, Applicants note the section of the patent cited by the Examiner in this regard (column 4, lines 39-45) is a discussion of how to make the device of Schalkhammer et al. and manners in which the size and number of islands can be varied. There is no discussion in Schalkhammer et al. related to variations in the number of islands from a functional standpoint. Indeed, in contrast to the Examiner's position, there is no suggestion that a single metal particle can be used in the device of Schalkhammer et al.

For these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. Rejection of Claims Under 35 U.S.C. §103

At paragraph 9 of the Office Action, claims 46-66 are rejected under 35 U.S.C. §103(a) as being obvious over Schalkhammer et al. in view of Natan et al. (USSN 6,149,868).

The Examiner states that while Schalkhammer et al. does not teach a system comprising a colloidal suspension of one or more metal particles, Natan et al. provides the missing element. The Examiner concludes that it would have been obvious to combine and substitute a system comprising a colloidal suspension of one or more metal particles of Natan et al. in the system of Schalkhammer et al., because Natan et al. states "in yet another embodiment, detection is accomplished at extremely low analyte concentrations." The Examiner explains that the ordinary practitioner would have been motivated to combine and substitute a system comprising a colloidal suspension in the system of Schalkhammer et al. to improve concentration determination and provide a system wherein detection is accomplished at extremely low analyte concentrations.

In response, Applicants note that Natan et al. discloses a nanometer-scale structure from which surface enhanced Raman scattering (SERS) measurements can be taken. More specifically, it discloses a sandwich of an analyte (such as a protein) between a colloidal metal nanoparticle and a SERS substrate (e.g., a macroscopic silver particle). Thus, the structure in Natan et al. is a combination of three elements, nanometer-sized metal particles, a biomolecule and a SERS substrate. It is the sandwich of these three elements that is the basis of the

invention. The improvements over the art are discussed in col. 2, lines 49-62. Use of this structure allows "exceedingly low" amounts of the analyte (see, e.g., col. 3, lines 5-8).

SERS measurements are based on vibrational spectral intensities of the biomolecule in the analyte. It appears that the sandwich structure of Natan et al. provides for an enhancement in the vibrational spectral intensities (col. 1, lines 16-20; col. 5, lines 40-56). Thus, it is the linkage between the three elements in Natan et al. that provides the improvement in detection.

The skilled artisan would not have been motivated to combine and substitute the colloidal suspension of metal particles of Natan et al. with the system of Schalkhammer et al. to arrive at the invention recited in claims 46-66. The linkage of the three elements in Natan et al. provides an apparent increase in the vibrational spectral intensities of biomolecules. There is no teaching or suggestion in Natan et al. that a colloidal suspension of metal particles can be used to induce expression of intrinsic (or extrinsic) fluorescence of a biomolecule. Further, it is not the use of the colloidal suspension that allows detection of extremely low concentrations of analyte in the structure of Natan et al. Rather, it is the use of the sandwich structure. Thus, there would have been no motivation to use a colloidal suspension of metal particles in the system of Schalkhammer et al. based on the disclosure of Natan et al.

For these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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